THERAPEUTIC AND PATHOGENIC APPROACHES FOR THE MUSCULAR DYSTROPHIES

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National Institute of Arthritis and Musculoskeletal and Skin Diseases
National Institute of Neurological Disorders and Stroke

THIS PA USES THE "MODULAR GRANT" AND "JUST-IN-TIME" CONCEPTS. IT INCLUDES DETAILED MODIFICATIONS TO THE STANDARD APPLICATION INSTRUCTIONS THAT MUST BE USED WHEN PREPARING APPLICATIONS IN RESPONSE TO THIS PA.

PURPOSE

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) and the National Institute of Neurological Disorders and Stroke (NINDS) encourage investigator-initiated research grant applications of therapeutic and pathogenic approaches for the muscular dystrophies. Responses to this program announcement may include studies in appropriate animal models or preclinical or clinical studies in patients with Duchenne muscular dystrophy (DMD), Becker muscular dystrophy (BMD), facioscapulohumeral dystrophy (FSHD), limb-girdle muscular dystrophy (LGMD), myotonic dystrophy (DM), congenital muscular dystrophy (CMD), Emery-Dreifuss muscular dystrophy (EMD), or other forms of muscular dystrophy.

HEALTHY PEOPLE 2010

The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2010," a PHS led national activity for setting priority areas. This PA is related to one or more of the priority areas. This program announcement, Therapeutic and Pathogenic Approaches for the Muscular Dystrophies, is related to the priority area chronic disabling conditions. Potential applicants may obtain a copy of "Healthy People 2010" at http://www.health.gov/healthypeople/.

ELIGIBILITY REQUIREMENTS

Applications may be submitted by domestic and foreign for-profit and non-profit organizations, public and private, such as universities, colleges, hospitals, laboratories, units of state and local

governments, and eligible agencies of the Federal government. Racial/ethnic minority individuals, women, and persons with disabilities are encouraged to apply as principal investigators.

MECHANISM OF SUPPORT

The mechanisms of support will be the individual research project grant (R01) and the program project grant (P01). The Principal Investigator or program director, as well as any participating investigators, will plan, direct, and perform the research. The total project period for an application submitted in response to this program announcement may not exceed five years.

For all competing individual research project grant (R01) applications requesting up to $250,000 direct costs per year, specific application instructions have been modified to reflect "MODULAR GRANT" and "JUST-IN-TIME" streamlining efforts being examined by NIH. Complete and detailed instructions and information on Modular Grant applications can be found at: http://grants.nih.gov/grants/funding/modular/modular.htm. Applications that request more than $250,000 in any year must use the standard PHS 398 (rev. 4/98) application instructions.

Applicants must receive permission from the NIAMS or NINDS prior to the submission of an application requesting more than $500,000 in direct costs per year for any year of the proposed study. In addition, applications for program project grants may only be submitted from domestic organizations and investigators are requested to contact the NIAMS or NINDS representative listed under INQUIRIES as early as possible in the planning stages.

FUNDS AVAILABLE

NIAMS and NINDS intend to commit approximately $ 5.0 million in total costs to fund competing applications submitted in response to this announcement during fiscal years 2002- 2004. Although the financial plans of NIAMS and NINDS provide support for this program, awards pursuant to this PA are contingent upon availability of funds and the receipt of a sufficient number of meritorious applications.

RESEARCH OBJECTIVES

Background

Muscular dystrophies collectively have a high impact on health, affecting tens of thousands of people in the United States alone. The diseases are characterized by weakness and wasting of

muscles. Many incidents of muscular dystrophy represent new occurrences of disease, where there is no prior family history. Though research has recently revealed much about genetic defects associated with many forms of muscular dystrophy, treatment for the diseases has not changed significantly. There is a need to learn more about pathogenesis of the diseases and ways to treat affected people.

Duchenne muscular dystrophy (DMD) is most common, affecting approximately one in 3,500 male births. This X-linked disease is characterized by muscle necrosis and regeneration. The regenerative process cannot maintain normal muscle tissue and mass, resulting in progressive muscle fiber loss. Affected boys usually must use wheelchairs by age 12, with death often occurring by age 20 from cardiac or respiratory problems. The genetic defect leads to missing or abnormal dystrophin, an important structural protein unknown until the gene was discovered. A milder variant, Becker muscular dystrophy (BMD), is caused by different defects in the DMD gene, that produce truncated but partially functional dystrophin. Symptoms are similar to DMD, with muscles
of the pelvis, upper arms, and upper legs affected first, but they are more variable than in DMD. Some affected individuals are able to walk only until early adulthood, others to an advanced age. Survival in some is to middle age but others have survived more than 80 years. Heart trouble may develop in early adulthood. The National Institute of Neurological Disorders and Stroke, the National Institute of Arthritis and Musculoskeletal and Skin Diseases and the Office of Rare Diseases sponsored a workshop on the Therapeutic Approaches for Duchenne Muscular Dystrophy (DMD), May 15-16, 2000 in Bethesda, MD. The goals of this workshop were to address key questions in improving treatments for DMD and identify areas of needed scientific knowledge, impediments, and critical next steps to promote effective therapy. A summary of the workshop may be found at: http://www.ninds.nih.gov/news_and_events/dmdmtngsummary.htm

Myotonic dystrophy (DM) is the most common form of muscular dystrophy in adults. It is dominantly inherited and, in addition to skeletal muscles, affects the brain, the lens of the eye, and the heart. Myotonic dystrophy is one of the growing number of triplet repeat disorders; it is associated with a CGT expansion in an untranslated region of 19q13.3. Larger numbers of repeats are found in more severely affected individuals, and the number of repeats tends to increase from generation to generation, thus explaining earlier age of onset and increased symptoms in subsequent generations (anticipation). The product of the myotonic dystrophy locus on chromosome 19 is a novel form of protein kinase. The function of this specific kinase is unknown, and it has yet to be determined whether a defect in this protein leads to the myotonic dystrophy phenotype.

Facioscapulohumeral (FSH) muscular dystrophy is an autosomal dominant form that initially affects muscles of the face (facio), scapula (scapulo) and upper arms (humeral). Symptoms may develop in early childhood and are usually noticeable in the teenage years. A progressive skeletal muscle weakness usually develops in other areas of the body as well; often the weakness is asymmetrical. Life expectancy is normal, but some affected individuals become severely disabled. Nearly all cases are associated with a distal 4q35 deletion. Because there are no known genes in this region, a novel position effect has been postulated to explain the disease phenotype. The National Institute of Arthritis and Musculoskeletal and Skin Diseases, the National Institute of Neurological Disorders and Stroke, and the Office of Rare Diseases sponsored a Conference on the Cause and Treatment of Facioscapulohumeral Muscular Dystrophy, held in Bethesda, MD on May 8-9, 2000. A summary of this meeting may be found at: http://www.nih.gov/niams/reports/fshdsummary.htm.

The limb-girdle muscular dystrophies (LGMD) are genetically heterogeneous, with both dominant and recessive forms reported. All limb-girdle muscular dystrophies show a similar distribution of muscle weakness, affecting both upper arms and legs. The recessive LGMDs are more frequent than the dominant forms, and usually have a childhood or teen-age onset. The dominant LGMDs usually show an adult onset. In addition to muscle weakness, the creatine kinase (CK) values are elevated in affected individuals, usually 4-10 times the normal laboratory values. Four of the recessive forms have been associated with defects in genes coding for the sarcoglycan complex, which, along with dystrophin, helps anchor muscles to the extracellular matrix. More devastating mutations in these same genes can cause severe childhood autosomal muscular dystrophy (SCARMD).

Emery-Dreifuss muscular dystrophy (EMD) is a sex-linked form characterized by wasting of shoulder, upper arm, and shin muscles. Joint deformities are common. It also inflicts serious cardiac problems that can result in premature and sudden death. Cardiac involvement may also cause premature death in female carriers. The responsible sex-linked gene has been located (Xq28), and it has been found to code for a previously unknown protein, called emerin, associated with the muscle membrane. Emerin is normally found in both skeletal and heart muscle. Different mutations of this gene may result in the absence of emerin and thus the disease. A few cases have been found in which emerin is normal, suggesting genetic heterogeneity.

Congenital muscular dystrophy (CMD) is a heterogeneous group of severe autosomal-recessive neuromuscular diseases with early clinical onsets. Manifestations of CMD are evident at birth or

in the first few months of life and consist of muscle weakness and hypotonia, delayed motor milestones, severe and early contractures, and, often, joint deformities. Some cases of CMD have been attributed to absence of merosin, a component of laminin. Laminin is the extracellular component of the complex that, together with dystrophin and associated glycoproteins, anchors the muscle cell. The same gene is responsible for one of the animal models of muscular dystrophy, the dy/dy mouse.

Although genes responsible for many forms of muscular dystrophy have been identified, much more research is needed to discover the pathogenic mechanisms involved and develop effective treatments.

Scope and Objectives

A principal goal of this initiative is to promote research that will lead to better treatment for the muscular dystrophies. The NIAMS and NINDS encourage investigator-initiated research grant applications to study therapeutic and pathogenic approaches. Important research priorities include studies on gene and stem cell therapies, pharmacological approaches to treatment, and clarification of the role of inflammatory mechanisms.

Responses to this program announcement may include studies in appropriate animal models or preclinical or clinical studies in patients. Investigators with diverse scientific interests are invited to apply their expertise to basic, applied, and clinical research to enhance our understanding of the pathogenesis and treatment of the muscular dystrophies, including the development and sharing of appropriate resources, including animal models.

Examples that illustrate possible areas of research are presented below. They are intended only to provide a broad direction for research and should be considered illustrative and not restrictive. Special emphasis is on areas discussed in the reports of the recent meetings held at the NIH on DMD and FSHD.

The following general examples are relevant to several forms of muscular dystrophy:

- examine genetic heterogeneity, and search for additional candidate genes;

- examine genotype/phenotype correlations within and between families;

- develop improved diagnostic procedures;

o improve imaging techniques to better diagnose and monitor muscle disease;

o study pathogenic mechanisms leading from gene defects to muscular dystrophy phenotypes;

o clarify the role of inflammatory changes that accompany tissue degeneration;

o explore further development of new types of therapy, including gene transfer and gene correction;

o study muscle stem cells and their therapeutic possibilities;

o explore pharmacologic interventions: evaluate current use of steroids;

o further pursue the development and sharing of appropriate animal models for muscular dystrophies;

o study the involvement of apoptotic cell death in the process of muscle fiber degeneration; and

o improve therapeutic value of protein expression from transplanted myoblasts.

Several examples of research needs in DMD, taken from the May 2000 meeting, are:

o characterize molecular aspects of the Duchenne muscular dystrophy population;

o clarify the role of inflammatory changes that accompany tissue degeneration;

o study the nature of the inflammatory changes that accompany degeneration in DMD;

o determine if the dystrophin-glycoprotein complex has both a mechanical and signaling role;

o examine the role of dystrophin-glycoprotein disruption in tissues other than striated muscle, such as retina, brain, and vascular tissues;

o improve techniques for possible gene transfer therapies, by optimizing the expression cassette, improving the design of viral vectors, clarifying and managing immunologic consequences, and optimizing gene delivery in terms of tissue targeting and efficiency of transfecting cells;

o expand studies on alternative (non-viral) approaches that target the endogenous dystrophin gene (gene correction through the use of chimeraplasts; exon skipping and mRNA splicing through the use of antisense oligonucleotides; and alteration of translation by suppression of stop codons through the use of aminoglycoside antibiotics);

o expand the use of muscle stem cells for possible therapy, through clarifying their origin and developmental state; find ways to identify and purify muscle stem cells; improve conditions for culturing and expanding cell populations; determine if stem cells can be delivered through the circulatory system efficiently and effectively; and

o explore pharmacological therapeutic approaches, including the role of anti-inflammatory agents, and determine mechanisms of action.

Several examples of research needs in FSHD, taken from the May 2000 meeting, are:

o determine basis of differential involvement of muscles, reflected by the regional pattern of disease. Comparison of muscle groups might show the cause of relative specificity of affected muscles. Comparing expression patterns of RNA and protein in affected and non-affected muscle will provide insights into alterations occurring as the disease progresses.

o explore the role of inflammation in FSHD. While FSHD has been described as the most inflammatory form of muscular dystrophy, there is no evidence that disease severity is lessened by administration of the anti-inflammatory drug prednisone. It is necessary to explore the relationship between inflammatory cells, muscle cell death, and blood vessels.

o Study properties of muscle cells derived from affected tissue. Cells cultured from FSHD muscle show increased sensitivity to oxidative stress. This needs to be followed up by studies verifying that this occurs in vivo and establishing how this cellular phenotype develops.

INCLUSION OF WOMEN AND MINORITIES IN RESEARCH INVOLVING HUMAN SUBJECTS

It is the policy of the NIH that women and members of minority groups and their subpopulations must be included in all NIH supported biomedical and behavioral research projects involving human subjects, unless a clear and compelling rationale and justification are provided that inclusion is inappropriate with respect to the health of the subjects or the purpose of

the research. This policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43).

All investigators proposing research involving human subjects should read the UPDATED "NIH Guidelines for Inclusion of Women and Minorities as Subjects in Clinical Research," published in the NIH Guide for Grants and Contracts on August 2, 2000 (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-048.html); a complete copy of the updated Guidelines is available at http://grants.nih.gov/grants/funding/women_min/guidelines_update.htm. The revisions relate to NIH defined Phase III clinical trials and require: a) all applications or proposals and/or protocols to provide a description of plans to conduct analyses, as appropriate, to address differences by sex/gender and/or racial/ethnic groups, including subgroups if applicable; and b) all investigators to report accrual, and to conduct and report analyses, as appropriate, by sex/gender and/or racial/ethnic group differences.

INCLUSION OF CHILDREN AS PARTICIPANTS IN RESEARCH INVOLVING HUMAN SUBJECTS

It is the policy of NIH that children (i.e., individuals under the age of 21) must be included in all human subjects research, conducted or supported by the NIH, unless there are scientific and ethical reasons not to include them. This policy applies to all initial (Type 1) applications submitted for receipt dates after October 1, 1998.

All investigators proposing research involving human subjects should read the "NIH Policy and Guidelines" on the Inclusion of Children as Participants in Research Involving Human Subjects that was published in the NIH Guide for Grants and Contracts, March 6, 1998, and is available at the following URL address: http://grants.nih.gov/grants/guide/notice-files/not98-024.html Investigators also may obtain copies of these policies from the program staff listed under INQUIRIES. Program staff may also provide additional relevant information concerning the policy.

URLS IN NIH GRANT APPLICATIONS OR APPENDICES

All applications and proposals for NIH funding must be self-contained within specified page limitations. Unless otherwise specified in an NIH solicitation, internet addresses (URLs) should not be used to provide information necessary to the review because reviewers are under no obligation to view the Internet sites. Reviewers are cautioned that their anonymity may

be compromised when they directly access an Internet site.

APPLICATION PROCEDURES

The research grant application form PHS 398 (rev. 4/98) is to be used in applying for these grants, with the modifications noted below. These forms are available at most institutional offices of sponsored research; from the Division of Extramural Outreach and Information Resources, National Institutes of Health, 6701 Rockledge Drive, MSC 7910, Bethesda, MD 20892-7910, telephone 301/435-0714, Email: grantsinfo@nih.gov; and on the internet at http://grants.nih.gov/grants/funding/phs398/phs398.html. Applications should be submitted at the standard times indicated in the application instructions.

Applicants planning to submit an investigator-initiated new (type 1), competing continuation (type 2), competing supplement, or any amended/revised version of the preceding grant application types requesting $500,000 or more in direct costs for any year are advised that he or she must contact the Institute or Center (IC) program staff before submitting the application, i.e., as plans for the study are being developed. Furthermore, the application must obtain agreement from the IC staff that the IC will accept the application for consideration for award. Finally, the applicant must identify, in a cover letter sent with the application, the staff member and Institute or Center who agreed to accept assignment of the application. This policy requires an applicant to obtain agreement for acceptance of both any such application and any such subsequent amendment. Refer to the NIH Guide for Grants and Contracts, March 20, 1998 at http://grants.nih.gov/grants/guide/notice-files/not98-030.html

Applicants for the program project grant (P01) should contact the NIAMS and NINDS program officers listed under INQUIRIES to discuss their planned projects and to request the Institute's guidelines for program project applications. Guidelines may be found at: http://www.nih.gov/niams/grants/Guidelines/guidelines.htm (NIAMS) and http://www.ninds.nih.gov/funding/ppg_guidelines.htm (NINDS).

SPECIFIC INSTRUCTIONS FOR MODULAR GRANT APPLICATIONS

BUDGET INSTRUCTIONS

Modular Grant applications will request direct costs in $25,000 modules, up to a total direct cost request of $250,000 per year. (Applications that request more than $250,000 direct costs in any year must follow the traditional PHS 398 application instructions.) The total direct costs must

be requested in accordance with the program guidelines and the modifications made to the standard PHS 398 application instructions described below:

PHS 398

o FACE PAGE: Items 7a and 7b should be completed, indicating Direct Costs (in $25,000 increments up to a maximum of $250,000) and Total Costs [Modular Total Direct plus Facilities and Administrative (F&A) costs] for the initial budget period Items 8a and 8b should be completed indicating the Direct and Total Costs for the entire proposed period of support.

o DETAILED BUDGET FOR THE INITIAL BUDGET PERIOD - Do not complete Form Page 4 of the PHS 398. It is not required and will not be accepted with the application.

o BUDGET FOR THE ENTIRE PROPOSED PERIOD OF SUPPORT - Do not complete the categorical budget table on Form Page 5 of the PHS 398. It is not required and will not be accepted with the application.

o NARRATIVE BUDGET JUSTIFICATION - Prepare a Modular Grant Budget Narrative page. (See http://grants.nih.gov/grants/funding/modular/modular.htm for sample pages.) At the top of the page, enter the total direct costs requested for each year. This is not a Form page.

o Under Personnel, list all project personnel, including their names, percent of effort, and roles on the project. No individual salary information should be provided. However, the applicant should use the NIH appropriation language salary cap and the NIH policy for graduate student compensation in developing the budget request.

For Consortium/Contractual costs, provide an estimate of total costs (direct plus facilities and administrative) for each year, each rounded to the nearest $1,000. List the individuals/organizations with whom consortium or contractual arrangements have been made, the percent effort of all personnel, and the role on the project. Indicate whether the collaborating institution is foreign or domestic. The total cost for a consortium/contractual arrangement is included in the overall requested modular direct cost amount. Include the Letter of Intent to establish a consortium. Provide an additional narrative budget justification for any variation in the number of modules requested.

o BIOGRAPHICAL SKETCH - The Biographical Sketch provides information used by reviewers in the assessment of each individual's qualifications for a specific role in the proposed project, as

well as to evaluate the overall qualifications of the research team. A biographical sketch is required for all key personnel, following the instructions below. No more than three pages may be used for each person. A sample biographical sketch may be viewed at: http://grants.nih.gov/grants/funding/modular/modular.htm

- Complete the educational block at the top of the form page;
- List position(s) and any honors;
- Provide information, including overall goals and responsibilities, on research projects ongoing or completed during the last three years.
- List selected peer-reviewed publications, with full citations;

o CHECKLIST - This page should be completed and submitted with the application. If the F&A rate agreement has been established, indicate the type of agreement and the date. All appropriate exclusions must be applied in the calculation of the F&A costs for the initial budget period and all future budget years.

o The applicant should provide the name and phone number of the individual to contact concerning fiscal and administrative issues if additional information is necessary following the initial review.

GENERAL INSTRUCTIONS

Check "YES" in item 2a on the face sheet of the application and type “Therapeutic and Pathogenic Approaches for the Muscular Dystrophies.”

Submit a signed, typewritten original of the application, including the Checklist, plus five signed photocopies, in one package to:

CENTER FOR SCIENTIFIC REVIEW
NATIONAL INSTITUTES OF HEALTH
6701 ROCKLEDGE DRIVE, ROOM 1040 - MSC 7710
BETHESDA, MD 20892-7710
BETHESDA, MD 20817 (for express/courier service)

If the application is for a program project, submit the original and three copies to the Center for Scientific Review. An additional two copies must be sent to the program director for the institute

that has agreed to accept, either Dr. Lymn or Dr. Spinella, at the addresses listed under INQUIRIES to expedite processing and review of applications for multi disciplinary efforts.

REVIEW CONSIDERATIONS

Applications will be assigned on the basis of established referral guidelines. Applications that are complete will be evaluated for scientific and technical merit by an appropriate scientific peer review group convened in accordance with NIH peer review procedures. As part of the initial merit review, all applications will receive a written critique and undergo a process in which only those applications deemed to have the highest scientific merit will be discussed, assigned a priority score, and receive a second level review by the National Advisory Council of the assigned Institute(s).

Review Criteria

The goals of NIH-supported research are to advance our understanding of biological systems, improve the control of disease, and enhance health. In the written review, comments on the following aspects of the application will be made in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals. Each of these criteria will be addressed and considered in the assignment of the overall score. Note that the application does not need to be strong in all categories to be judged likely to have major scientific impact and thus deserve a high priority score. For example, an investigator may propose to carry out important work that by its nature is not innovative but is essential to move a field forward.

o Significance: Does this study address an important problem? If the aims of the application are achieved, how will scientific knowledge be advanced? What will be the effect of these studies on the concepts or methods that drive this field?

o Approach: Are the conceptual framework, design, methods, and analyses adequately developed, well integrated, and appropriate to the aims of the project? Does the applicant acknowledge potential problem areas and consider alternative tactics?

o Innovation: Does the project employ novel concepts, approaches or methods? Are the aims original and innovative? Does the project challenge existing paradigms or develop new methodologies or technologies?

o Investigator: Is the investigator appropriately trained and well suited to carry out this work? Is the work proposed appropriate to the experience level of the principal investigator and other researchers (if any)?

o Environment: Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environment or employ useful collaborative arrangements? Is there evidence of institutional support?

In addition to the above criteria, in accordance with NIH policy, all applications will also be reviewed with respect to the following:

o The adequacy of plans to include both genders, minorities and their subgroups, and children as appropriate for the scientific goals of the research. Plans for the recruitment and retention of subjects will also be evaluated.

o The reasonableness of the proposed budget and duration in relation to the proposed research

o The adequacy of the proposed protection for humans, animals or the environment, to the extent they may be adversely affected by the project proposed in the application.

o Review of grants with foreign components will consider availability of special opportunities for furthering research programs through the use of unusual talent resources, populations, or environmental conditions in other countries which are not readily available in the United States or which provide augmentation of existing United States resources.

o For program project grant applications, additional factors to be considered during the review would include the efficacy of the collaboration, the commitment of the participants to the collaboration, the design and responsibilities of the coordinating center and the cost effectiveness of the collaborative effort.

AWARD CRITERIA

Applications will compete for available funds within the annual set-aside mentioned under FUNDS AVAILABLE. Beyond the limits of the set-aside applications will compete with all other approved applications. The following will be used in making funding decisions:

o Scientific and technical merit of the proposed project as determined by peer review

o Availability of funds

o Program balance among research areas of the announcement

NIAMS funding policy may be seen at: http://www.nih.gov/niams/grants/payline2.htm. NINDS funding strategy may be found at: http://www.ninds.nih.gov/funding/ninds_funding_strategy.htm

INQUIRIES

Inquiries concerning this PA are encouraged. The opportunity to clarify any issues or questions from potential applicants is welcome.

Direct inquiries regarding programmatic and scientific issues to one of the following persons:

Richard W. Lymn, Ph.D.
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Giovanna M. Spinella, M.D.
Neurogenetics and Neurodevelopment
National Institute of Neurological Disorders and Stroke
6001 Executive Boulevard, Room 2132
Bethesda, MD 20892
Telephone: (301) 496-5745
FAX: (301) 402-1501
Email: gs41b@nih.gov

Direct inquiries regarding fiscal matters to:

Melinda Nelson
Grants Management Officer
National Institute of Arthritis and Musculoskeletal and Skin Diseases
45 Center Drive, Room 5AS-49F, MSC 6500
Bethesda, MD 20892-6500
Telephone: (301) 594-3535
FAX: (301) 480-5450
Email: nelsonm@mail.nih.gov

Karen D. Shields
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Telephone: (301) 496-9231
FAX: (301) 402-0219
Email: ks26n@nih.gov

AUTHORITY AND REGULATIONS

This program is described in the Catalog of Federal Domestic Assistance No. 93.846 (NIAMS) and No. 93.853 (NINDS). Awards are made under authorization of sections 301 and 405 of the Public Health Service Act as amended (42 USC 241 and 284) and administered under NIH grants policies and Federal Regulations 42 CFR 52 and 45 CFR Parts 74 and 92. This program is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review.

The PHS strongly encourages all grant and contract recipients to provide a smoke free workplace and promote the non-use of all tobacco products. In addition, Public law 103-227, the pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care or early childhood development services are provided children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

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